Preparation, Characterization, and *In-Vitro* Evaluation of Telmisartan Inclusion Complexes with Modified β-Cyclodextrins using Microwave Irradiation and Response Surface Methodology

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Abstract— Telmisartan (TEL) is an angiotensin II receptor antagonist used for the management of hypertension. TEL belongs to a BCS class II drug with low water solubility and, thereby, low bioavailability. The present work is focused on improving the dissolution rate of TEL by complexation with modified β-cyclodextrins like such as sulfobutyl ether β-cyclodextrin (SBE7-β-CD) and methyl-β-cyclodextrin (Me-β-CD). The phase solubility studies indicated an AL type curve, so the complexes of TEL with modified cyclodextrin were prepared with a 1:1 molar ratio. The microwave irradiation method was used for the preparation of inclusion complexes. In order to maximize drug content, optimization of the process variables was achieved through the use of response surface methodology involved in the preparation of inclusion complexes. The prepared inclusion complexes of TLE (SMWT 3 and MMWT 3) were characterized. The inclusion complex SMWT 3 showed a 4.13 folds' increase in dissolution rate, whereas MMWT 3 showed a 3.94-fold increase compared to pure TEL. The FTIR showed no interaction between TEL and modified cyclodextrins. The X-RD and DSC results prove the formation of inclusion complexes and the transformation of crystalline to amorphous TEL during complexation. The SEM images showed that TEL morphology changed completely after complexation. All the results obtained suggest that the preparation of inclusion complexes of TEL with modified β-cyclodextrins is a promising approach for improving bioavailability.

Keywords: Telmisartan, 3^2 Factorial Design, sulfobutyl ether β-cyclodextrin (SBE_7-β-CD), Methyl-β-cyclodextrin (Me-β-CD), Microwave irradiation, Bioavailability.

I. INTRODUCTION

The angiotensin II type 1 receptor blocker telmisartan (TEL) is used to treat hypertension [1]. The compound has the empirical formula $C_{33}H_{30}N_4O_2$ and a molecular weight of 514.62 g/mol. It is a crystalline powder that is white to pale yellow and almost completely insoluble in water [2]. The Biopharmaceutical Classification System classifies the drug as class-II [3]. Because of the drug's pH-dependent predicted solubility and its 0.09 µg/ml water solubility, its oral bioavailability is restricted and variable, ranging from 42 to 58% [4, 5]. Although several methods for improving water-insoluble drug physicochemical and biological properties have drawbacks, complexing the drug with cyclodextrins is one of the more promising approaches. Cyclodextrins are multiglucopyranose oligosaccharides. Cyclodextrins can form lipophilic drug inclusion complexes with lipophilic drugs due to their hydrophilic shell and lipophilic core [6]. Cyclodextrins improve drug solubility when complexed with drugs [7]. In the literature, it was found that TEL inclusion complexes with β-CD and HP-β-CD, solubility and dissolution can be enhanced [8]. However, cyclodextrin formulations are limited by toxicological concerns. Since the discovery of modified cylodextrins like sulfobutyl ether β-cyclodextrin (SBE_7-β-CD) and methyl-β-cyclodextrin (Me-β-CD) with lower toxicity, there has been more interest in using cyclodextrins, especially to make drugs dissolve, stay stable, and be more bioavailable. [9, 10]. SBE_7-β-CD is a cyclic hydrophilic oligosaccharide that is negatively charged in water. Solubility in water is much higher than β-CD at room temperature (70 g/100 ml). In addition, there is no nephrotoxicity, which is a problem with β-CD [11]. Me-β-CD has a considerable advantage over β-CD as a host molecule since it is more soluble than β-CD, i.e., 100 mg/ml and 0.18 g/ml, respectively [12]. It is thought that the higher solubility of (Me-β-CD) in water will help the drug dissolve effectively when it is complexed [13, 14]. Because of these advantages, SBE7-β-CD and Me-β-CD could improve the physical and chemical properties of drugs that don't dissolve well in water. Traditionally, there are many ways to make inclusion complexes. Some of these methods are co-evaporation, drying by spray, or drying by freezing. All of these approaches have two major problems: they take a long time and require a lot of organic solvent. Microwave irradiation (MWI), a new technology, is being looked into as a way to avoid the problems with current complexation methods. On the other hand, MWI will have less trouble when it comes to scaling up [15, 16]. This study synthesises inclusion compounds with optimised process parameters and investigates TEL dissolution with modified cyclodextrins.

II. MATERIALS AND METHODS

A. Materials

Hyderabad-based Aurobindo Pharma Limited provides telmisartan as a gift sample. SBE7-β-CD is obtained from Chembest Research Laboratories Limited, China and Methyl-β-cyclodextrin from Hyderabad-based BLD Pharmtech Pvt Ltd. All other substances including solvents were analytical.

B. Analysis of drug content

We dissolved a 10 mg TEL complex in 100 ml of 0.1 M hydrochloric acid. After filtering the solution, the TEL concentration was determined using a UV spectrophotometer set at 296 nm [17].

C. Phase solubility studies

Regarding TEL and modified cyclodextrin stochiometry, phase solubility studies are performed. The Higuchi-Connors technique was used to measure the phase solubility of cyclodextrins and TEL [18]. In different stoppered conical flasks, an excess of TEL was added to 10 ml of phosphate buffer pH 7.5 containing various increased concentrations of Me-β-CD or SBE_7-β-CD. After 24 hours, the suspension

was shaken, filtered, diluted, and analysed. We calculated Ks from equation [19].

$$Ks = \frac{slope}{So(1 - slope)}$$

Where S_0 is the TEL aqueous solubility.

D. *Preparation Inclusion complexes*

1) *Preparation of Physical mixtures*

On the basis of the preliminary phase solubility studies, a mixture of TEL and either of the modified cyclodextrins was made in a molar ratio of 1:1. The physical mixture (PM) was created by merely mixing accurately weighed quantities with a spatula in a mortar for two minutes.

2) *Kneading method*

The complexes were prepared by kneading preweighed amounts of TEL and cyclodextrins in a mortar for 20 minutes. After adding a few drops of ethanol, the final mixture was kneaded for an additional 45 minutes. After mixing, the paste was dehydrated in a vacuum desiccator overnight. After making it through sieve number 60, the dried product was collected [20].

3) *Synthesis of TEL and modified cyclodextrins Inclusion compounds by microwave irradiation*

a) *Preliminary trials*

Understanding the process variables is crucial for producing inclusion compounds. A 1:1 molar mixture of TEL and either modified cyclodextrin with a small amount of ethanol was microwaved. The minimum power required for the reaction is 200 W for 10 seconds, and charring is observed at 300 seconds, whereas charring occurs in 250 seconds at 700 W. In both situations, the amount of solvent is held constant. The samples exposed to radiation were dried in a desiccator [21, 22].

b) *Optimization of process variables*

Preliminary trials determined an independent variable processing range. An experimental design was utilised in order to investigate the impact that certain processing parameters, such as power and reaction time, have on the overall outcome [23]. A 3^2 factorial design was used to optimise the process parameters. We selected two independent variables, microwave power (X_1) from 200 to 600 W, reaction time (X_2) from 10 to 240 sec, and drug content (R) as the dependent variable. This polynomial equation describes how independent factors affect dependent variables [24]:

$$R = \alpha_0 + \alpha_1 X_1 + \alpha_2 X_2 + \alpha_{12} X_1 X_2 + \alpha_{11} X_1^2 + \alpha_{22} X_{22}^2$$

In the above equation, R represents the dependent variable. The mean of nine iterations, which is also the intercept, is equal to α_0. The values α_1, α_2, α_{12}, α_{11}, and α_{22} represent the estimated variable coefficients X_1, X_2, X_1X_2, X_{12}, and X_{22}, respectively. The coefficient was significant if $p < 0.05$. The significance of the model was assessed using a one-way analysis of variance ($p < 0.05$) [25].

c) *Verification of Optimisation Capability*

The optimisation potential of the mathematical model was evaluated using numerical optimisation (which is based on the concept of desirability) of the 3^2-factorial design findings. An optimum procedure was created by limiting the range of possible values for each input and output. The optimal ranges of the factors were limited to $200 \leq X_1 \leq 600$ W and $10 \leq X_2 \leq 240$ sec; while the response

ranges were 85 - 98 %. The % relative error was computed as follows [24, 25]:

$$\% \text{ Error} = \frac{\text{Experimental value} - \text{Predicted value}}{\text{Predicted value}} \text{ X } 100$$

E. In-vitro dissolution studies

The rates of TEL and TEL inclusion systems' dissolution were measured under sink conditions in 900 ml of phosphate buffer pH 7.5. The dissolution studies were conducted employing a dissolving rate test device of type 2 USP XXIII, and in the test, paddled at a rate of 75 rpm were employed for 30 minutes at a 37±0.5 °C. An amount containing 40 mg equivalent of TEL equivalent was placed in each basket. A 0.45 µm nylon disc filter was used to filter a five ml aliquot taken at various times. In cases where it was necessary to do so, the samples were diluted before being subjected to spectrophotometric analysis at 296 nm.

F. Characterization of inclusion complexes

The pure TEL, physical mixture, kneading complex, and microwave irradiated complexes were studied using FTIR spectra [26], differential scanning calorimetry analysis (30-300°C) [27], powder X-ray diffraction scanning range 0–90° [28], and scanning electron microscopy studies [29] using standard procedures.

III. RESULTS AND DISCUSSION OF THE EXPERIMENTS

G. Phase solubility studies

A phase solubility diagram for TEL using SBE_7-β-CD and Me-β-CD is shown in Figure 1. The pure TEL (S_0) was 6.1 µg/ml. Over the entire concentration range studied, TEL's solubility rises linearly as the concentration of modified -cyclodextrin rises, indicating an A_L-type diagram. Thus, a 1:1 inclusion complex was made. The estimated Ks for the TEL Me-β-CD inclusion complex was 935 ± 0.21 M^{-1} and for the TEL SBE_7-β-CD inclusion complex was 1807.32 ± 1.54 M^{-1}. So, we can say that TEL and SBE_7-β-CD make more stable complexes.

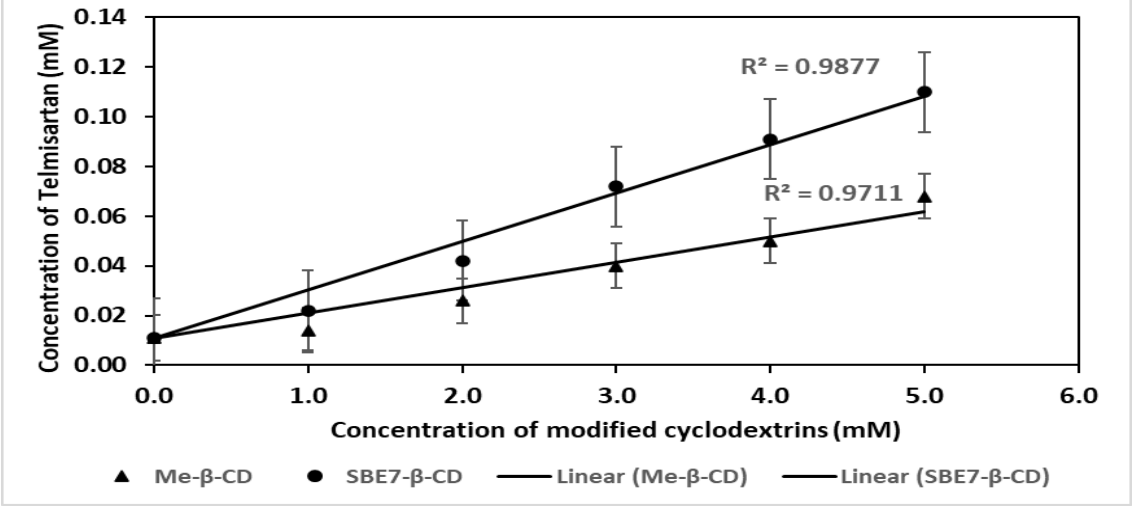

Fig. 1 Phase solubility studies of telmisartan with modified cyclodextrins

H. Analysis of drug content

The effect of all of the independent variables taken together on response was investigated using Stat Ease Design Expert 12. The intricate blending and kneading processes of SBE_7-β-CD show percentage drug content 98.9±0.65, 97.7±0.75 respectively (n=3) whereas for Me-β-CD is 98.75±0.71, 97.88±0.56. The medication content of nine TEL inclusion complexes with modified cyclodextrins was determined. The findings are presented in Table 1.

Table 1: 3^2 factorial TEL inclusion matrix; (n=3)

S.NO	Levels of independent variables employed		TEL SBE_7-β-CD Inclusion Complex	TEL Me-β-CD Inclusion Complex
Run	X_1: Power (W)	X_2: Time (Sec)	% Drug content	% Drug content
1	400	125	85.46 ± 0.42	65.25 ± 0.45
2	200	10	35.96 ± 0.65	20.25 ± 0.95
3	600	125	88.65 ± 0.17	80.29 ± 0.32
4	200	240	55.00 ± 0.58	60.45 ± 0.64
5	600	10	70.98 ± 0.94	45.45 ± 0.75
6	400	240	95.14 ± 0.48	98.63 ± 0.65
7	200	125	45.45 ± 0.69	40.63 ± 0.98
8	400	10	68.23 ± 0.74	35.74 ± 0.74
9	600	240	98.75 ± 0.36	98.36 ± 0.39

I. Experimental design and statistical data analysis

The quadratic model found a statistically significant ($p < 0.05$) relationship between drug content and sets of inclusions that have been prepared. Microwave-irradiated TEL inclusion complexes with SBE_7-β-CD have a polynomial equation for % drug content is

$$R_1 = 84.33 + 20.17\ X_1 + 12.5\ X_2 + 2\ X_1X_2 - 17.5\ X_1^2 - 2.5\ X_2^2$$

While all other factors are constant, coefficient estimates estimate response change per factor value change. The adjusted R^2 of 0.9930 is pretty close to the predicted R^2 of 0.9699. P-values for model terms that are less than 0.05 are considered to be statistically significant. The percentage of drugs can be significantly impacted by X_1, X_2, and X_1^2.

The polynomial equation that describes the relationship between the amount of drug in TEL inclusion complexes made with Me-β-CD using microwave irradiation is

$$R_2 = 68.04 + 17.13\ X_1 + 26.00\ X_2 + 3.18X_1X_2 - 8.97\ X_1^2 - 2.24\ X_2^2$$

While all other factors are constant, coefficient estimates estimate response change per factor value change. The difference between the predicted R^2 of 0.7594 and the adjusted R^2 of 0.944 is less than 0.2. Significant model terms have P-values below 0.05. X_1 and X_2 affect % drug content.

A response surface method was utilised to analyse the relationship between independent factors and responses. Three-dimensional response surface plots are used to depict the main effects of the independent variables, shown in Figure 2.

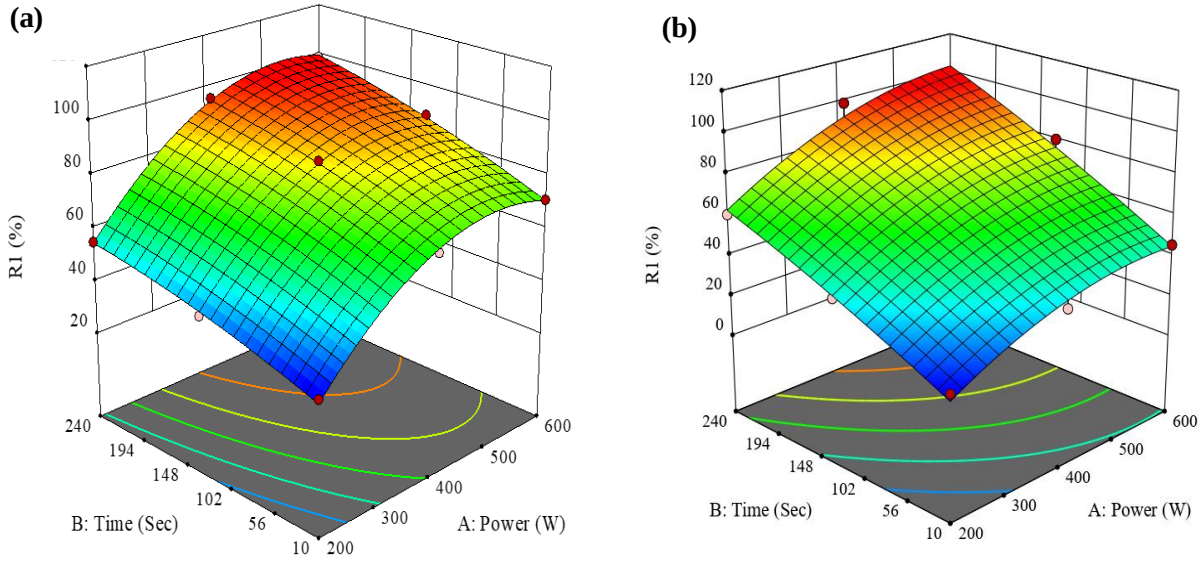

Fig. 2 Three-dimensional surface graphs showing how process factors affect drug content (a) TEL SBE_7-β-CD complex 3D surface plot (b) TEL Me-β-CD complex 3D surface plot

J. Process optimisation

After setting limits on each input and output, the programme suggested several sets of independent variable ratios. The optimisation capabilities of the model were evaluated using three different inclusion ratios. Numerical optimization was carried out based on the desirability function of selected solutions, which was found to be 1. Based on their attributes, these three batches' observed values were very similar to the software-predicted values displayed in Table 2. Reliably predicting process variables, factorial models exhibit error rates between 0.73 and 2.29 percent, which is the lowest error. The inclusion complexes SMWT 3 and MMWT 3 that had been made were characterised.

Table 2: Optimising inclusion complex preparation process variables

Responses	Batch	X_1 Power(W)	X_2 Time (Sec)	Observed Value (Mean± SD, n=3)	Predicted Value	% Error
Drug content in SBE7-β-CD irradiated inclusion complexes	SMWT 1	400	230	95.20 ± 0.15	93.70	1.60
	SMWT 2	400	223	95.40 ± 0.61	93.26	2.29
	SMWT 3	400	215	93.50 ± 0.26	92.82	0.73
Drug content in Me-β-CD irradiated inclusion complexes	MMWT 1	400	232	91.72 ± 0.32	90.26	1.61
	MMWT 2	400	227	90.89 ± 0.45	89.40	1.66
	MMWT 3	400	223	89.50 ± 0.98	88.63	0.98

K. *In-vitro dissolution studies*

The dissolution curves of the TEL and all TEL inclusion complexes are displayed in Figure 3. According to these findings, the complexes produced by physical blend and kneading inclusion dissolved more completely than the pure drug. The TEL SBE_7-β-CD inclusion complexes (SMWT 3), shows a higher rate of dissolution in comparison to that of the physical mixture and kneading inclusion complex. In the case of inclusion complexes prepared by Me-β-CD inclusion complex (MMWT 3), they showed a higher rate compared to physical mixtures and kneading complexes. The solubilization, amorphization, and improved wettability that result from microwave irradiated inclusion complexes help to increase the dissolving rate. The microwave irradiation method enhances the dissolution rate of TEL by 4.13 folds by complexation with SBE_7-β-CD whereas in the case of Me-β-CD complexation, it is 3.94 folds.

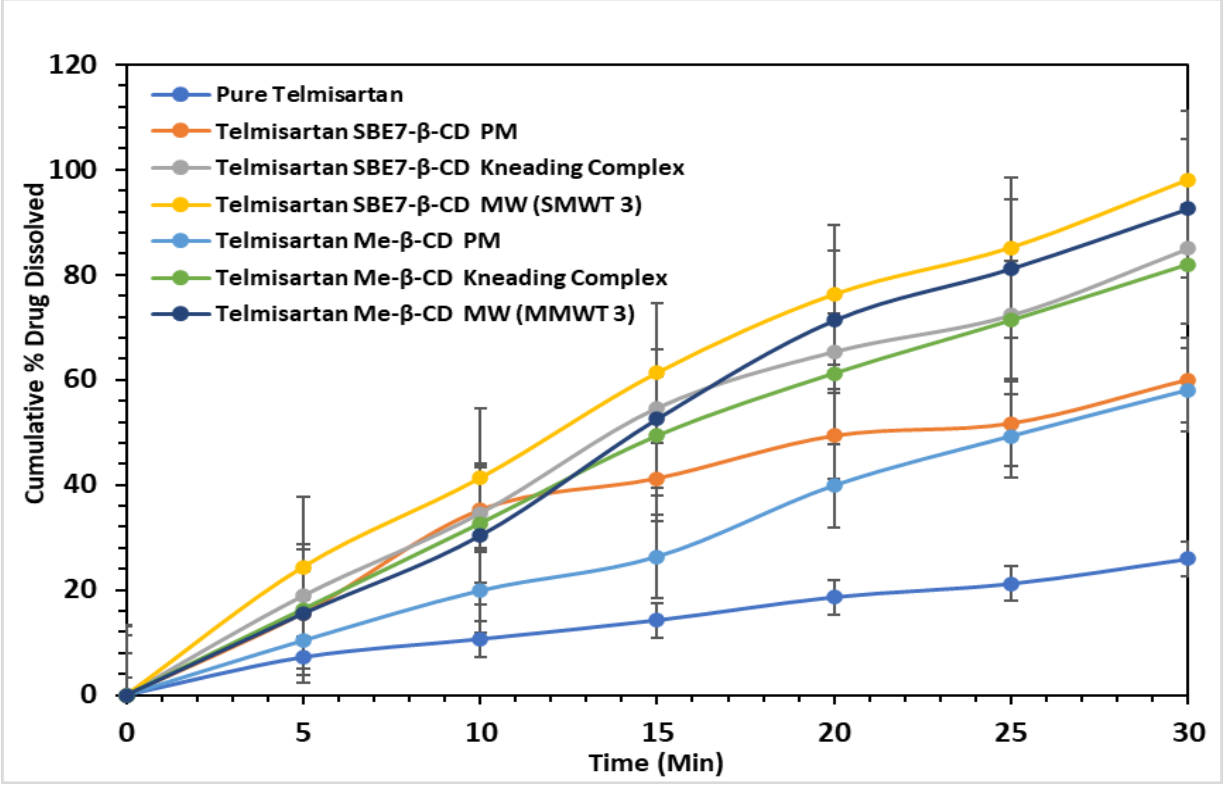

Fig. 3 Dissolution profiles of TEL and TEL cyclodextrin complexes.

L. *Fourier Transform Infrared Spectroscopy*

Figure 4 shows TEL and prepared complexes FTIR spectra. TEL has a characteristic moderate peak at 3058 cm^{-1} for aromatic C-H bond stretching vibration, a moderate peak at 2956 cm^{-1} for aliphatic C-H bond stretching of aromatic ring, a steep apex at 1690 cm^{-1} for C = O bond stretching of carbonyl group, a peak at 1615 cm^{-1} for C=N stretching vibration, a peak at 1599 for C = C bending and stretching vibrations, a peak at 1458 for C-H bending, a peak at 1382 for O-H bending, and a peak at 1262 cm^{-1} for C-N stretching vibrations. Complexes had identical peaks but slightly varied wavelengths, indicating no interaction.

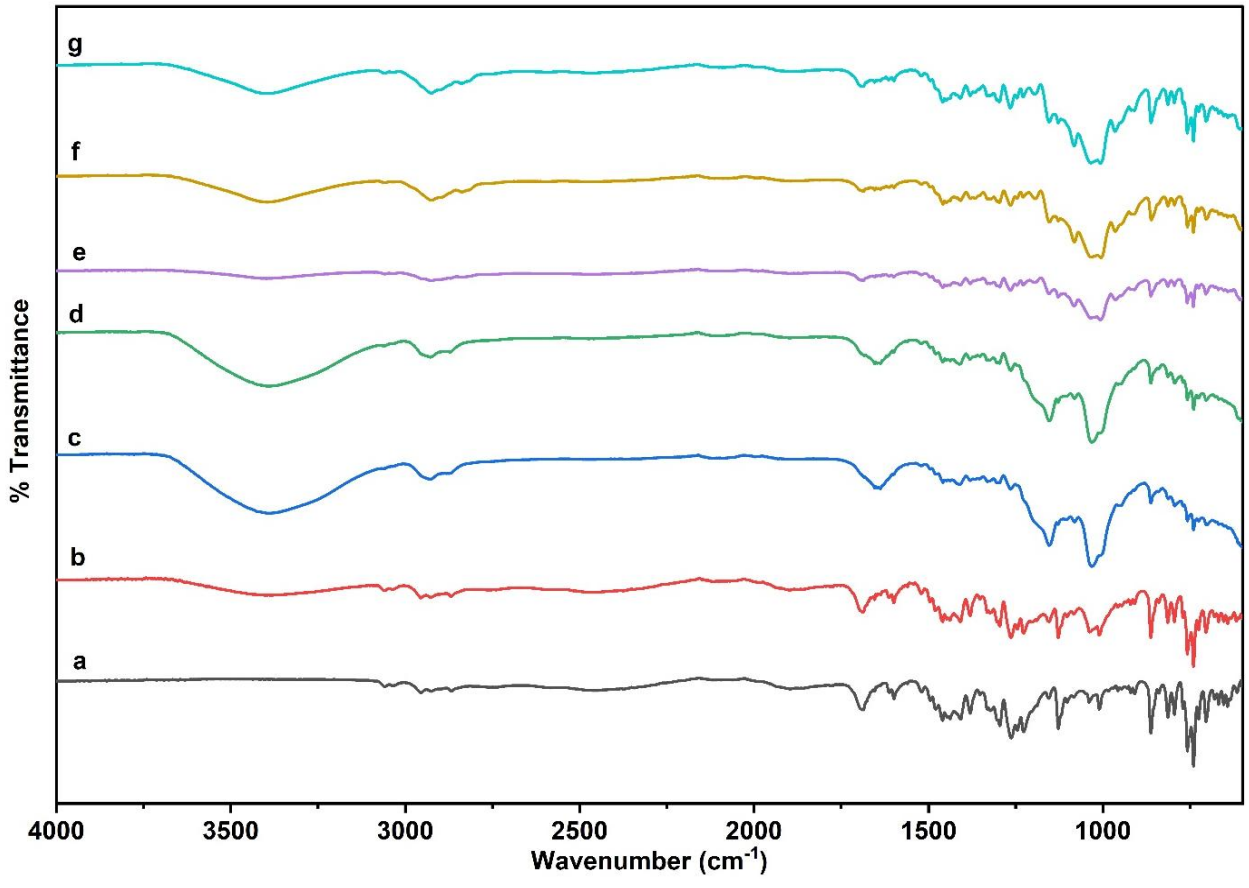

Fig. 4: FTIR spectra of (a) Telmisartan (b) Telmisartan SBE7-β-CD PM (c) Telmisartan SBE7-β-CD PM Kneading complex (d) Telmisartan SBE7-β-CD MW complex (e) Telmisartan Me-β-CD PM (f) Telmisartan Me-β-CD Kneading complex (g) Telmisartan Me-β-CD MW complex

M. Thermal analysis

The differential scanning calorimetric curve of TEL and inclusion complexes, shown in Figure 5, gave information about the solid-state interactions and the influence of preparation methods. TEL differential scanning calorimetry data revealed an endothermic peak that is relatively sharp at 270.5°C, resembling the value reported in the literature [30]. SBE_7-β-CD showed a broad endothermic peak at 275°C [31, 32]. The physical mixture of TEL and SBE_7-β-CD shows both the peaks representing the drug and SBE_7-β-CD. In the kneading thermogram, both the TEL and SBE_7-β-CD peaks had decreased intensities, with a peak at 268.9°C, implying little interaction between them. The SMWT 3 showed a broad endothermic peak with a 36°C start and a 108°C finish, indicating the formation of an inclusion complex. The thermogram of methyl-β-cyclodextrin revealed a broad endothermic peak from 45°C to 111°C. The physical blend of TEL and Me-β-CD shows both the peaks representing the drug and Me-β-CD. The kneading thermogram of TEL and Me-β-CD showed a peak at 257°C, indicating interaction and complex formation. A peak at 212.5°C was observed in the microwave-irradiated complex of TEL Me-β-CD, indicating complex formation.

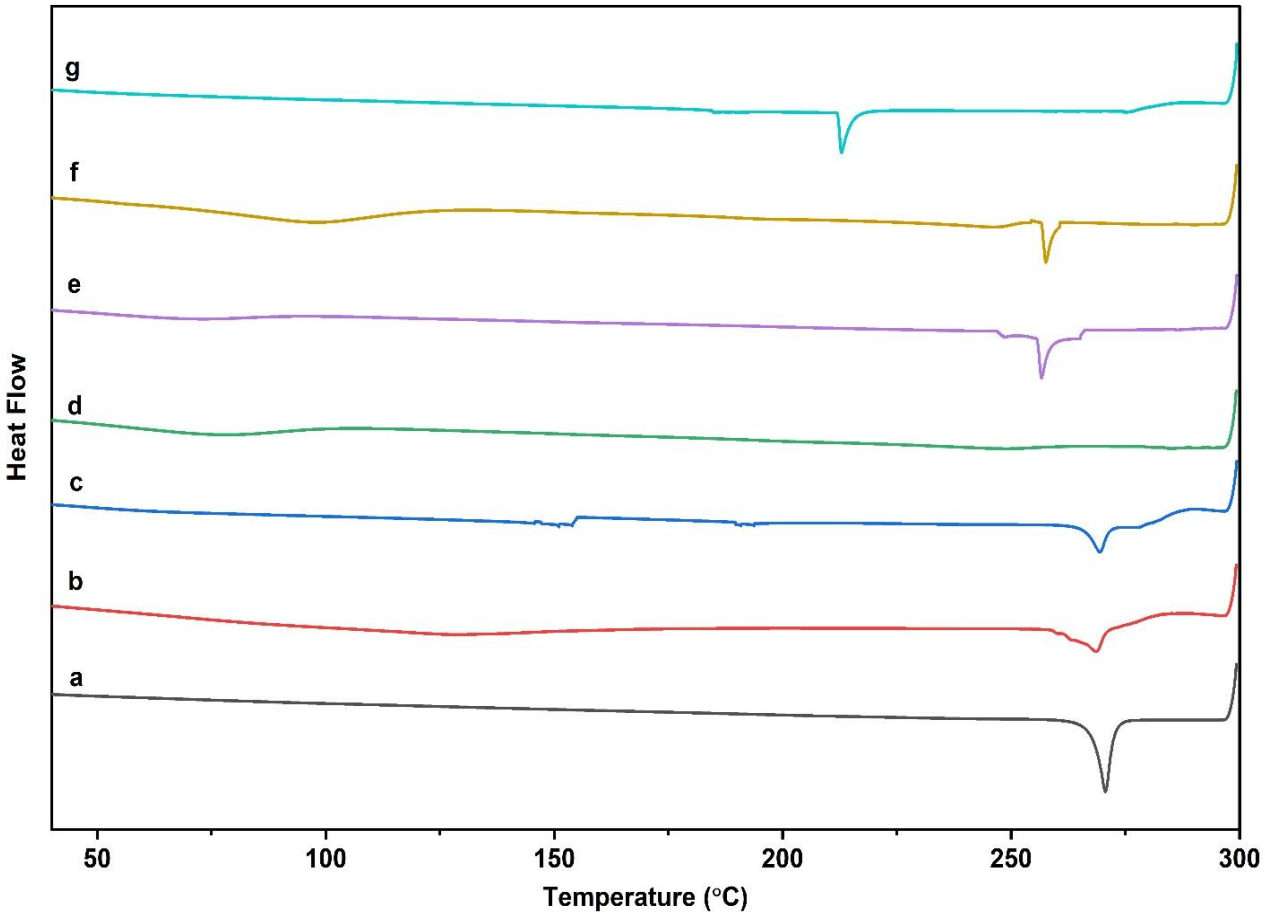

Fig. 5: DSC thermograms of (a) Telmisartan (b) Telmisartan SBE7-β -CD PM (c) Telmisartan SBE7-β-CD PM Kneading complex (d) Telmisartan SBE7-β-CD MW complex (e) Telmisartan Me-β-CD PM (f) Telmisartan Me-β-CD Kneading complex (g) Telmisartan Me-β-CD MW complex

N. Powder X-ray diffraction

The X-ray diffraction studies were used to look into the crystal structure of TEL in complexes., as shown in Figure 6. The TEL showed crystalline sharp peaks at 6.63°, 9.08°, 10.46°, 12.42°, 13.98°, 14.9°, 16.9°, 17.26°, 18.36°, 18.91°, 20.02°, 21.27°, 22.25°, 23.63°, 24.73°, 27.92°, and 30.98° (2θ) with a crystallinity index of 70 %. The results are similar to published data [33]. SBE_7-β-CD shows a diffraction pattern indicative of a crystalline nature. The physical mixture of TEL SBE_7-β-CD shows a similar diffraction pattern as that of pure TEL, with a slight variation in intensity. The SBE_7-β-CD kneading complex showed peaks at 7.27°, 12.54°, 14.75°, 18.79°, 19.46°, 22.65°, 23.78°, 24.88°, 25.0°, 25.43°, 28.38°, and 31.53° with a crystallinity index of 49.3%. The microwave irradiation complex of SBE_7-β-CD peaks at 6.72°, 12.12°, 14.75°, 18.51°, 19.89°, 21.82°, 22.80°, 24.61°, 25.56°, 28.77°, and 31.25° with a crystallinity index of 46.51%. Me-β-CD showed a diffraction pattern indicative of its amorphous nature. The physical mixture of TEL Me-β-CD shows a similar diffraction pattern as that of pure TEL with a slight variation in intensity. The Me-β-CD kneading complex showed peaks at 6.72°, 8.65°, 9.78°, 11.01°, 11.56°, 12.27°, 14.2°, 17.38°, 18.36°, 19.06°, 20.32°, 22.52°, 24.05°, 25.16°,

27.09°, 28.10°, and 31.25° with a crystallinity index of 63%. The microwave irradiation complex of Me-β-CD peaks at 6.87°, 11.44°, 12.69°, 14.35°, 17.38°, 18.51°, 19.46°, 21.27°, 22.37°, 23.23°, 24.33°, 25.28°, 27.09°, 27.92°, and 31.40° with a crystallinity index of 64%. The TEL degree of crystallinity was found to be 70.0%. The complex of TEL SBE_7-β-CD microwave-irradiated was 46.51 percent, while the complex of TEL Me-β-CD is 64 percent.

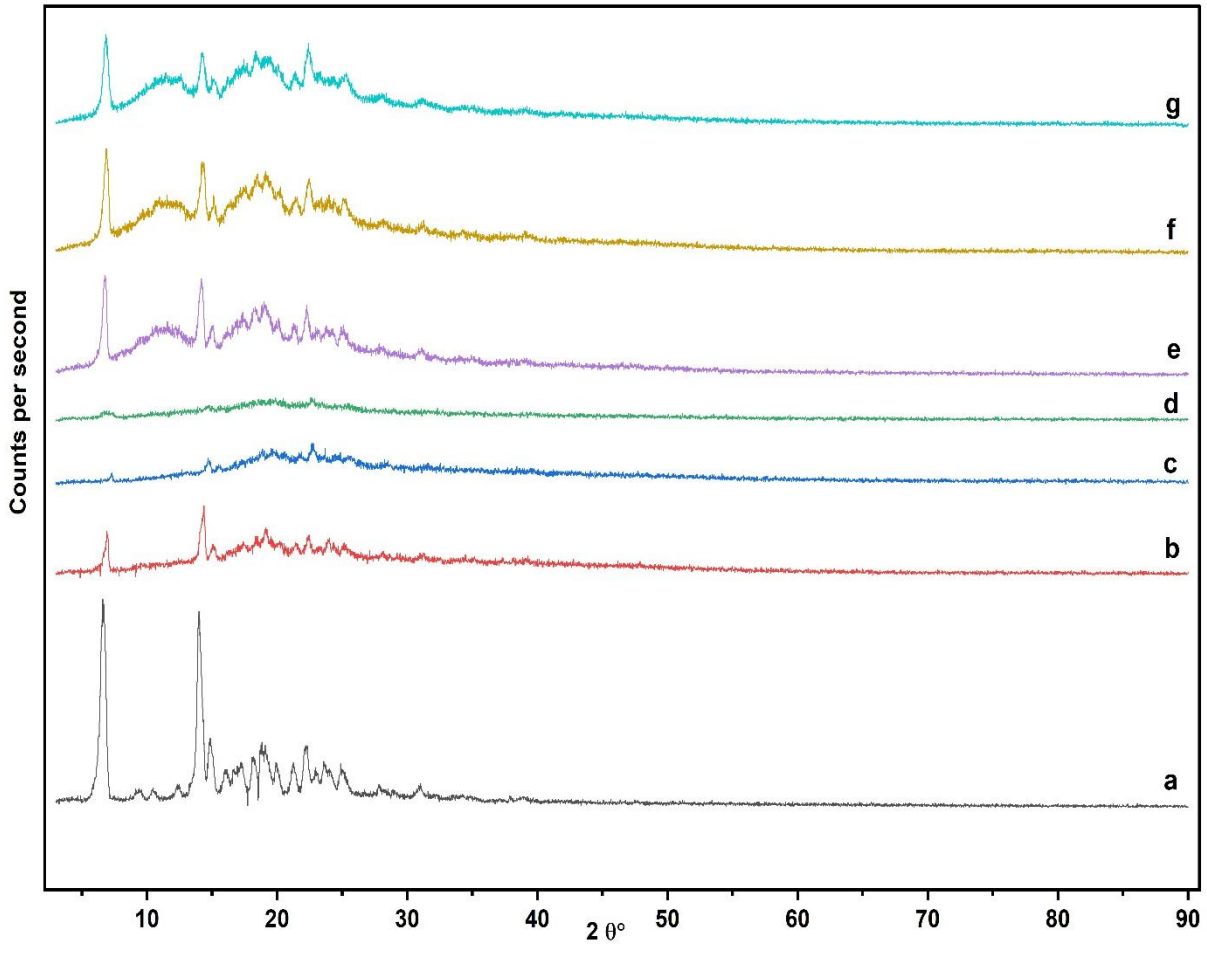

Fig. 6: X-RD plots of (a) Telmisartan (b) Telmisartan SBE7-β -CD PM (c) Telmisartan SBE7-β-CD PM Kneading complex (d) Telmisartan SBE7-β-CD MW complex (e) Telmisartan Me-β-CD PM (f) Telmisartan Me-β-CD Kneading complex (g) Telmisartan Me-β-CD MW complex

O. Scanning Electron Microscopy studies

Figure 7 shows SEM morphology and particle size of TEL, kneading, and microwave-irradiated complexes. TEL crystals were rod-shaped. TEL crystals bonded to SBE_7-β-CD particles in a physical combination, indicating no solid-state interaction. TEL SBE_7-β-CD kneading complex interacted slightly. The TEL SBE_7-β-CD microwave irradiation compound produced huge, irregular-shaped amorphous particles. Me-β-CD particles shrunk, smoothed, and lost shape after inclusion complexation.

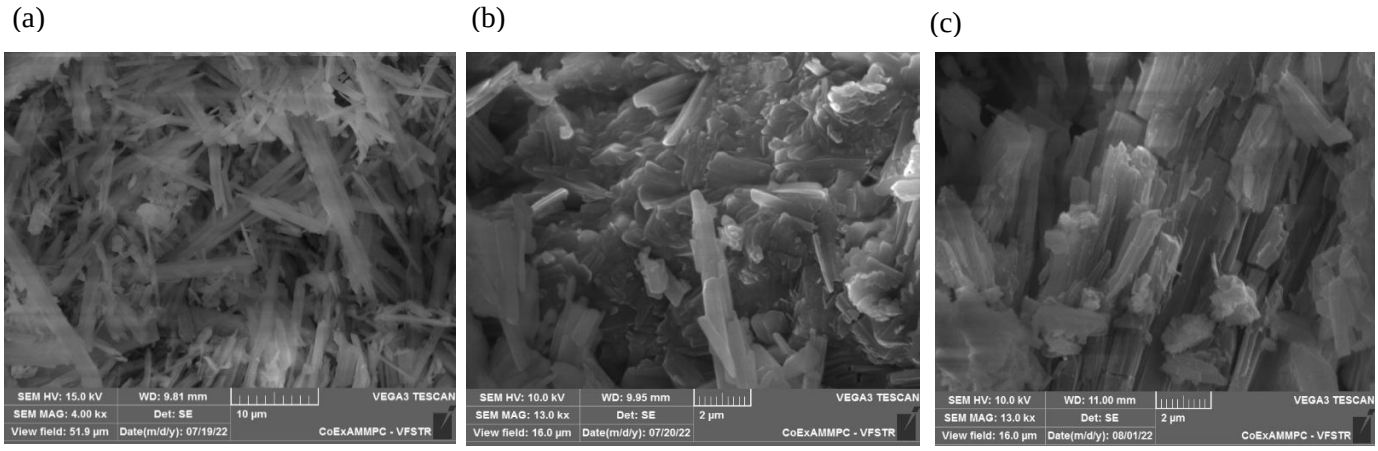

Fig. 7: SEM image of (a) Pure Telmisartan (b) TEL SBE_7-β-CD Microwave Irradiated Complex (c) TEL ME-β-CD Microwave Irradiated Complex

IV. CONCLUSION

TEL was rendered more soluble in this work by the addition of modified cyclodextrins. Based on phase solubility studies, we used a 1:1 molar ratio to make our inclusion complexes. Kneading and microwave irradiation were the two approaches that were utilised in the process of producing TEL inclusion complexes with SBE_7-β-CD and Me-β-CD. Using a 3^2-factorial design, the variables in the irradiation method for generating TEL inclusion complexes were optimised. This allowed for maximum efficiency in the preparation of the complexes. Further testing and characterisation of the produced inclusion complexes SMWT 3 and MMWT 3 were carried out. Dissolution rates of TEL inclusion complexes with SBE_7-β-CD formed by kneading technique were 3.61 folds higher than those of pure TEL, while those using microwave irradiation technique (SMWC 3) were 4.17 folds higher, where the Me-β-CD complexes showed 3.48 and 3.94 folds, respectively. Solid-state interaction was indicated by DSC thermographs of microwave-irradiated complexes, and amorphization of TEL was discovered by X-ray diffraction. The FTIR spectra show that the typical peaks of functional groups have not changed noticeably. Evidence for a new solid phase as a result of complex formation was provided by scanning electron microscopy (SEM) images of SMWT 3 and MMWT 3 inclusion complexes. Thus, this combination improves TEL oral bioavailability in an appropriate dosage form.

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